

# Treatment of nonpsychotic major depression during pregnancy: patient safety and challenges

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**Abstract:** In pregnant women with major depression, the overarching goal of treatment is to achieve or maintain maternal euthymia, thus limiting both maternal and fetal exposure to the harmful effects of untreated or incompletely treated depression. However, the absence of uniformly effective therapies with guaranteed obstetric and fetal safety makes the treatment of major depression during pregnancy among the most formidable of clinical challenges. Clinicians and patients are still faced with conflicting data and expert opinion regarding the reproductive safety of antidepressants in pregnancy, as well as large gaps in our understanding of the effectiveness of most antidepressants and nonpharmacological alternatives for treating antenatal depression. In this paper, we provide a clinically focused review of the available information on potential maternal and fetal risks of untreated maternal depression during pregnancy, the effectiveness of interventions for maternal depression during pregnancy, and potential obstetric, fetal, and neonatal risks associated with antenatal antidepressant use.

**Keywords:** depression, major depressive disorder, pregnancy, antidepressants, safety

## Introduction

Major depression and other unipolar depressive syndromes are highly prevalent and disproportionately affect women.<sup>1,2</sup> The peak incidence of major depression in women is during the reproductive years,<sup>3</sup> raising the possibility of depressive episode onset (or relapse in women already diagnosed with major depression) during pregnancy. Indeed, the prevalence of any depressive illness during pregnancy is estimated at 18.4% (7.3% for major depressive disorder during pregnancy).<sup>4</sup> Rates of mood-disorder onset in women are roughly equivalent between pregnant and nonpregnant samples,<sup>5,6</sup> and the frequency of major depression during the second and third trimesters may even exceed that of the general population.<sup>7</sup>

Although major depression and other depressive illnesses cannot be cured at present, their symptoms can be controlled in most patients with focused psychotherapy, appropriate pharmacotherapy, or the combination of the two.<sup>8</sup> In pregnant women with major depression, the overarching goal of treatment is to achieve or maintain maternal euthymia, thus limiting both maternal and fetal exposure to the harmful effects of untreated or incompletely treated depression. Ideally, this would be achieved using treatment modalities that have no possibility of harming the pregnancy or developing fetus. Effective nonpharmacological modalities may achieve these aims for many, but not all, women with depression. Indeed, a considerable number of women benefit from antidepressant treatments for achieving or maintaining euthymia during pregnancy. On the other hand, the use of antidepressants for treating maternal depression and other

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disorders during pregnancy has increased steadily in the last two decades,<sup>9–13</sup> which has raised concerns about the risks versus benefits of this practice.

The absence of uniformly effective therapeutics with guaranteed obstetric and fetal safety makes the treatment of major depression during pregnancy among the most formidable of clinical challenges.<sup>14</sup> Clinical practice guidelines can provide direction, but to follow these guidelines clinicians must translate estimates of treatment effectiveness and risk from rapidly evolving population-level data to individual patients, taking into account each patient's tolerance of risk related to both the underlying illness and available interventions.<sup>15,16</sup> Clinicians and patients are still faced with conflicting data and expert opinion regarding the reproductive safety of antidepressants in pregnancy, as well as gaps in our understanding of the effectiveness of most antidepressants and nonpharmacological alternatives for treating antenatal depression. This paper provides a clinically focused review of the available information on risks of untreated maternal depression during pregnancy, effectiveness of interventions for maternal depression during pregnancy, and potential harms of treatments for maternal depression during pregnancy, and presents recommendations for treating maternal depression during pregnancy.

## Materials and methods

Relevant studies were identified via a Medline/PubMed search of the literature for reports and studies for the period beginning in 1996 and ending in 2013. Potential harms of interest included congenital malformations, adverse neonatal events, and obstetric complications. We used combinations of keywords that defined antidepressant exposures (antidepressants, selective serotonin-reuptake inhibitors [SSRIs], fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, bupropion, tricyclic antidepressants [TCAs], imipramine, desipramine, amitriptyline, nortriptyline, clomipramine, protriptyline, trimipramine, doxepin, monoamine oxidase inhibitors, phenelzine, tranylcypromine, isocarboxazid, mirtazapine, nefazodone, and vilazodone) with those that defined outcomes of interest (pregnancy outcome [congenital, fetal], birth outcome, malformations, congenital malformations, birth defects, cardiac/heart defects, persistent pulmonary hypertension of the newborn [PPHN], and neurobehavioral outcomes). Vortioxetine was not included because of its very recent regulatory approval. Milnacipran was not included because of its approval for treating fibromyalgia syndrome and limited clinical use for treating major depression. A similar

approach was used to locate reports addressing benefits and harms of nonpharmacological treatments (psychotherapy, interpersonal therapy [IPT], cognitive behavioral therapy [CBT], electroconvulsive therapy [ECT], repetitive transcranial magnetic stimulation [rTMS], exercise, bright-light therapy [luminotherapy], therapeutic massage, and acupuncture). Systematic reviews, meta-analyses, randomized trials, and observational studies were reviewed. Additional papers and abstracts were retrieved from the bibliographic sections of review papers and individual reports. Throughout the paper, we generally refer to maternal depression during pregnancy as “antenatal depression” (as opposed to “antenatal major depression”), because several of the reviewed studies included persons with clinically significant depressive symptoms but unconfirmed major depressive disorder diagnoses and because of variability in diagnostic methods across studies restricted to major depression.

## Results

### Clinical impact of antenatal depression

Antenatal depression has been linked with worse general health status; poor maternal self-care during pregnancy; underutilization of prenatal care; increased maternal use of cigarettes, alcohol, and other abused substances; isolation or withdrawal from family or other supports; and increased risk of postpartum depression and maternal suicide,<sup>17–23</sup> the latter of which may account for up to 20% of postpartum deaths.<sup>24</sup> Other potential risks of untreated antenatal depression include poor nutrition intake during pregnancy, severe fatigue, and lack of motivation for self-care.<sup>25</sup> Women with depression or other psychiatric disorders for which antidepressants are often prescribed are less likely to get appropriate prenatal and pediatric care, which may increase the risk of increased postneonatal morbidity.<sup>26,27</sup>

Untreated or undertreated antenatal depression has also been associated with a variety of adverse obstetric and neonatal outcomes, including preeclampsia and eclampsia,<sup>28,29</sup> miscarriage,<sup>30</sup> preterm birth or shorter gestational length,<sup>6,30–32</sup> poor fetal and infant growth,<sup>33–35</sup> low infant birth weight/small for gestational age,<sup>6,30,31,36,37</sup> and low Apgar scores.<sup>38</sup> A recent meta-analysis of 30 heterogeneous studies showed a modest association between antenatal depression and increased risk of premature delivery (odds ratio [OR] 1.37, 95% confidence interval [CI] 1.04–1.81) and decreased likelihood of breastfeeding initiation (OR 0.68, 95% CI 0.61–0.76).<sup>39</sup> The meta-analysis did not demonstrate a statistically significant increased risk of most other perinatal outcomes in association with antenatal depression; however, antenatal

depression was significantly but modestly associated with low birth weight (OR 1.39, 95% CI 1.00–1.94) and pre-eclampsia (OR 2.50, 95% CI 1.13–5.54) after restricting the analyses to adjusted data.

Maternal depression during pregnancy or the postpartum period has been associated with impaired mother–infant attachment and developmental difficulties in offspring.<sup>40</sup> Children exposed to untreated antenatal depression are at higher risk for developmental delay, impaired language development, and lower intelligence quotient (IQ) scores,<sup>41–43</sup> and poor socioemotional development, including worse emotional regulation and higher rates of depressive and anxiety symptoms.<sup>44–46</sup> Others have shown that approximately a third of school-age children experience depressive, anxiety, or disruptive disorders while their mother is depressed.<sup>47</sup>

On the other hand, successful treatment of antenatal depression is associated with reduced psychiatric symptoms and diagnoses in their children. In a cohort of 151 mother–child pairs who participated in the STAR\*D-Child (Sequenced Treatment Alternatives to Relieve Depression – Child) study, remission of maternal depression after 3 months of medication treatment occurred in 33% of subjects<sup>48</sup> and was associated with an 11% decrease in the rates of an affective, anxiety, or disruptive behavior disorders in offspring (aged 7–17 years), as assessed by the Kiddie Schedule for Disorders and Schizophrenia. Continuing depression was associated with an 8% increase in the rates of these diagnoses. The relationship between improvement in maternal depression and lower rates of child psychopathology and functioning were still apparent after 1 year of follow-up.<sup>49</sup>

## Effectiveness of treatments for antenatal depression

Clinicians, patients, and their families have a wide range of treatments from which to choose. Common treatments include pharmacotherapy, psychotherapy, and other therapies.

### Pharmacotherapy

The effectiveness of antidepressants for treating antenatal depression or preventing depressive relapse in women with depression during pregnancy has received limited investigation. In a nonrandomized, multicenter, prospective study of 201 antidepressant-treated patients (161 [81.1%] of whom were treated with SSRIs) recruited from specialty mental health treatment settings who were euthymic for at least 3 months prior to study entry, Cohen et al reported that discontinuation of antidepressants during pregnancy was associated with more frequent relapses (68% versus 26%)

compared with women who continued their medication.<sup>50</sup> Women who stopped effective antidepressant treatment had five times the risk of relapse. Of those who stopped antidepressant treatment but restarted medication, the overall risk of relapse was also decreased, but to a smaller degree than patients who received continuous treatment throughout pregnancy. Lowering the dose of antidepressant did not reduce the risk of relapse. Relapses occurred more often in depressed patients with markers of more severe illness, including longer duration of illness, greater number of lifetime episodes, history of suicidal ideation, and family history of depressive illness.

A small prospective cohort study of 238 depressed pregnant women, 71 of whom were treated with SSRIs, reported that mean depressive symptom levels (as measured by the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement and the 17-item version of the Hamilton Depression Rating Scale) in women with continuous depression during pregnancy and no SSRI treatment were significantly greater than exposure groups that consisted of depressed women who received SSRI treatment. The study authors suggest that the results were consistent with the “expected treatment effects of SSRIs”, presumably in comparison with nonpuerperal major depression.<sup>51</sup>

It is currently unclear if antidepressant effectiveness is the same for treating puerperal and nonpuerperal major depression, and questions remain regarding the effectiveness of antidepressant treatment for preventing depressive relapses during pregnancy in women with established diagnoses of major depression.<sup>15</sup> In the Cohen et al study, women who chose to continue an effective antidepressant throughout pregnancy still had a 26% risk of relapse during follow-up.<sup>50</sup> Moreover, in a well-controlled study of 778 women with a history of any depressive disorder (as determined by lay interviewers using the Composite International Diagnostic Interview) who were recruited from obstetric rather than specialty mental health care settings, the risk of a major depressive episode during pregnancy did not differ statistically between women who took antidepressants and those who did not (hazard ratio 0.85, 95% CI 0.52–1.40).<sup>52</sup> The overall rate of major depressive episode onset during pregnancy was 16%, though differences by antidepressant exposure in rates of depressive episode occurrence were not reported, and the analyses were not stratified by depression severity or presence of comorbid illnesses, such as anxiety disorders.

Therefore, it seems clear that some pregnant women with antenatal depression will benefit from antidepressant treatment, but a substantial proportion of patients will not. This is

broadly consistent with findings from studies of antidepressant effectiveness in the broader population of patients with nonpuerperal major depression. Comparative effectiveness studies of antidepressants for treating antenatal depression are lacking, and additional studies are needed to determine the effectiveness of antidepressants for treating antenatal depression across treatment settings. This would not only permit better estimates of antidepressant effectiveness overall and by individual agent, but would also have the potential to inform clinical practice by helping determine which patients are most likely to benefit from specific antidepressant medications during pregnancy.

### Psychotherapy

There is evidence from controlled studies that systematically oriented psychotherapies, such as IPT and CBT, may be effective for treating antenatal depression or clinically significant depressive symptoms that occur during pregnancy.

#### Interpersonal therapy

A recent meta-analysis of 24 studies (18 of which focused on individual IPT and six of which focused on relational therapies) in pregnant or postpartum women with depression demonstrated significant positive effects on depressive symptoms.<sup>53</sup> Treatment-effect sizes were larger with individual IPT than relational therapies (such as marital and family therapies). Interventions that included an IPT component were also found to have greater effect sizes for reducing depressive symptom levels in another systematic review and meta-analysis of 27 heterogeneous studies that examined the effectiveness of pharmacologic and psychological interventions for unipolar depression during pregnancy or the postpartum.<sup>54</sup> Partner-assisted IPT, a form of IPT that was specifically developed for perinatal depression, showed promising results in a preliminary proof-of-concept trial in women with antenatal or postpartum depression.<sup>55</sup>

#### Cognitive behavioral therapy

Although CBT is an established treatment for mild-to-moderate nonpuerperal major depression, far less is known about its effectiveness for treating antenatal depression. The same meta-analysis of 27 heterogeneous studies reviewed earlier found CBT to be beneficial for perinatal depression, albeit with small-to-medium effects.<sup>54</sup> In a randomized trial, CBT adapted for perinatal depression in outpatients was associated with greater improvement in depressive symptoms than standard care over 16 weeks of follow-up.<sup>56</sup> Most individual trials of CBT for perinatal depression have focused

on the treatment of postpartum depression.<sup>57–59</sup> Therefore, additional investigations of the effectiveness of CBT for treating antenatal depression are needed.

#### Other psychotherapies

Difficulties with marital, family, and other important relationships are common complications of mood disorders in general, and are robust predictors of depression during pregnancy and the postpartum period.<sup>60</sup> It is therefore surprising that there has been so little investigation of the effectiveness of relational therapies (focused on marital and family problems) for treating antenatal depression. One meta-analysis reviewed earlier showed lower effect sizes with relational therapies than IPT in women with antenatal depression;<sup>53</sup> however, it seems reasonable that cases of maternal depression in which marital and family problems contribute heavily to depressive symptom burden may also stand to benefit most from these interventions as well as IPT. The effectiveness of psychodynamic psychotherapy and psychoanalytic approaches in this population is described only in case literature.<sup>61</sup>

#### Other nonpharmacological interventions

##### Exercise

Physical exercise during pregnancy is associated with improved cardiorespiratory fitness and other health benefits, without evidence of harm to the newborn.<sup>62</sup> While not generally considered to be a stand-alone treatment for depression, exercise has been shown to help alleviate symptoms of major depression in nonpregnant samples.<sup>63–65</sup> One study showed that supervised aerobic exercise commenced at 16–20 weeks gestation and extended over 3 months resulted in reduced depressive symptoms in nulliparous women with no psychiatric history.<sup>66</sup> Results of two small studies suggest that significant decreases in depressive symptoms can occur in women who were previously inactive.<sup>67,68</sup> Controlled studies of the benefits of exercise as either a primary or adjunctive intervention for treating antenatal depression are needed.

##### Luminotherapy

Luminotherapy, or bright-light therapy, is effective for seasonal and nonseasonal depression, though effect sizes for nonseasonal depression are smaller.<sup>69,70</sup> In an open trial of 16 women with antenatal depression, early morning bright light (60 minutes at 10,000 lx) was associated with a 49% decrease in depressive symptoms over 3 weeks.<sup>71</sup> Further improvement was observed in seven patients who continued early morning bright-light therapy for 5 weeks. An initial randomized trial of ten patients with antenatal

depression showed a higher positive response rate with luminotherapy delivered at 7,000 lx than a placebo condition consisting of subtherapeutic light exposure (60% versus 41%); however, these differences were not statistically significant.<sup>72</sup> In a larger randomized trial, significantly higher rates of positive treatment response were observed with luminotherapy (7,000 lx bright light) than placebo (70 lx dim red light) over 5 weeks (81.3% versus 45.5%).<sup>73</sup> Large, randomized trials are needed to establish the antidepressive effect of luminotherapy for treating antenatal depression.

#### Repetitive transcranial magnetic stimulation

One open-label study of ten women with antenatal depression who received 20 daily rTMS treatments, with or without concomitant antidepressants, showed a 70% positive treatment-response rate.<sup>74</sup> A larger study of 30 antenatally depressed patients who received rTMS over the left prefrontal cortex (6 days weekly for 3 weeks) showed significant reduction from baseline in Hamilton Depression Rating Scale scores. Rates of response and remission were 41.4% and 20.7%, respectively.<sup>75</sup> No adverse pregnancy or fetal outcomes were reported in either study. Randomized trials are needed to establish the antidepressive effect of rTMS for treating antenatal depression.

#### Electroconvulsive therapy

ECT is an established therapeutic modality for severe, catatonic, or psychotic depression, where rapid antidepressive effects are urgently required and lag time to therapeutic benefit associated with pharmacotherapy may be unacceptable. Extensive case-series data provide much of the rationale for the effectiveness and safety of ECT during pregnancy.<sup>76,77</sup> Although ECT has been used safely during all three trimesters of pregnancy and no consistent patterns of fetal or birth complications have been reported,<sup>76,78</sup> the anesthetic agents and neuromuscular blockers that are commonly employed as part of modern ECT techniques undergo transplacental passage, and case literature suggests that reduced fetal heart rate, uterine contractions, and premature labor may be adverse effects of ECT given in late pregnancy.<sup>79</sup> Randomized trials are lacking.

#### Complementary/alternative medicine treatments

There are very few high-quality studies of massage therapy, acupuncture, and hypnosis for treating antenatal depression.<sup>80,81</sup> One randomized trial compared acupuncture (specific for depression), control acupuncture, and massage for 8 weeks in 150 women with antenatal depression. Acupuncture specific

for depression was associated with significantly greater reduction in depressive symptoms than control acupuncture alone, or the two control conditions combined.<sup>82</sup> Rates of positive treatment response were also significantly higher with acupuncture specific for depression (63.0%) than the combined control conditions (44.3%).

## Potential harms of treatments for maternal depression

Potential harms of treatments for maternal depression have been best studied with respect to pharmacotherapies in general and antidepressants in particular. Therefore, the current review focuses on antidepressant pharmacotherapy. Table 1 presents a summary of the current US Food and Drug Administration (FDA) pregnancy-safety categories and listing of the safety category for commonly used antidepressants. Much less is known about the risks and benefits of psychotherapy or other therapies for antenatal depression.

#### Major congenital malformations

Major congenital malformations (MCMs) refer to structural defects present at birth that are associated with significant medical or cosmetic problems. In the US general population, the risk of MCMs is about one in every 33 infants (~3%).<sup>83</sup> The majority of birth defects have no known etiology, while approximately a quarter are attributed to genetic, chromosomal, or cytogenetic disorders.<sup>84</sup> Only 2%–3% of birth defects are classified as teratogen-induced.<sup>84</sup> For most MCMs, the sensitive period during embryonic development occurs during the 3–8 weeks after conception, or 5–10 weeks after the last maternal menstrual period. Teratogenic drugs act by drug-specific mechanisms on developing cells and tissues, and will typically cause organ-specific defects in a consistent pattern, rather than “any” malformation.<sup>85</sup>

Prior to 2000, small prospective studies showed no increased risk of MCMs in humans after in utero exposure to SSRIs,<sup>86–90</sup> the most common type of antidepressant used during pregnancy.<sup>91</sup> However, most MCMs are rare events, and prospective studies generally lack sufficient statistical power to detect subtle but potentially important increases in teratogenic risk. Very large observational studies using pregnancy registries or automated health outcome databases can provide useful information for estimating drug–MCM associations for antidepressants.

Most individual studies have considered fetal exposure to antidepressants as a single group or in broad classes (SSRIs, etc). The majority of individual studies have not

**Table 1** Summary of the current US Food and Drug Administration (FDA) pregnancy safety categories

Category	Definition	Antidepressants by FDA pregnancy-safety category
A	Adequate and well-controlled studies in pregnant women have not demonstrated fetal risk with exposure in the first trimester of pregnancy, and there is no evidence of risk with exposure in the second or third trimesters.	None
B	There are no adequate and well-controlled studies in pregnant women, and animal studies have not shown evidence of fetal risk.	Tetracyclic antidepressants: maprotiline
C	There are no adequate and well-controlled studies in pregnant women, but animal studies have shown evidence of fetal risk. For pregnant women, potential benefits may warrant use of the medication in pregnant women despite possible risks.	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline SNRIs: desvenlafaxine, duloxetine, venlafaxine TCAs: amitriptyline, amoxapine, clomipramine, doxepin, trimipramine MAOIs: isocarboxazid, phenelzine, selegiline, tranylcypromine Miscellaneous: bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine
D	There is positive evidence of human fetal risk based on investigational or postmarketing experience, but potential benefits may warrant use of the medication in pregnant women despite possible risks.	SSRIs: paroxetine TCAs: imipramine, nortriptyline
X	Animal or human studies have shown fetal abnormalities and/or there is positive evidence of human fetal risk based on investigational or postmarketing experience; risks from the medication clearly outweigh potential benefit.	None
N	The FDA has not classified the medication.	TCAs: desipramine, protriptyline

**Abbreviations:** SSRIs, selective serotonin-reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors.

demonstrated increased risk of MCMs associated with antidepressant exposure in the first trimester or at any time during pregnancy.<sup>87,89,92–104</sup> Meta-analyses of studies investigating the risk of antidepressants and “any” or “overall” MCMs have shown either small but statistically significant risk<sup>105,106</sup> or absence of significant increase in risk (Table 2).<sup>107–110</sup>

Studies with larger cohorts have shown an association between first trimester antidepressant exposure and congenital heart defects, particularly septal defects.<sup>93,94,98,111–117</sup> Although these results have not been replicated in several other studies,<sup>51,87,90,97,100,118–124</sup> a small increase in the risk of any cardiac malformation or septal heart defect has been consistently reported across meta-analyses (Table 3), particularly for paroxetine,<sup>105–107</sup> and in one case fluoxetine.<sup>108</sup> An increased risk of heart defects when SSRIs were combined with benzodiazepines during pregnancy compared with no first trimester exposure to drugs in either class (adjusted rate difference = 1.18%, 95% CI 0.18%–2.18%) has also been reported.<sup>115</sup> Neither drug class was associated with increased risk of heart defects when given individually.

Fewer studies of MCM risk with first trimester exposure to non-SSRI antidepressants exist. One analysis of birth registry data from Sweden examined the risk of congenital heart defects associated with maternal antidepressant use, including the use of TCAs, SSRIs, and serotonin-

norepinephrine reuptake inhibitors (SNRIs), during early pregnancy, and reported an increased risk of ventricular or atrial septal defects with clomipramine (OR 2.22, 95% CI 1.29–3.82) and paroxetine (OR 2.29, 95% CI 1.28–4.09).<sup>117</sup> These results supported earlier findings by the same authors of an increased risk for any cardiovascular defect associated with early pregnancy exposure to TCAs, primarily clomipramine (OR 1.77, 95% CI 1.07–2.91).<sup>125</sup> A third study by the same group reported an increased risk of congenital heart disease in the offspring of 1,029 women who reported use of clomipramine during early pregnancy (OR 1.87, 95% CI 1.16–2.99).<sup>98</sup> Very little information on the teratogenic risk associated with other TCAs is available, though most studies have been negative.<sup>126</sup> A report from the Bupropion Pregnancy Registry maintained by the drug manufacturer documented birth outcomes among 1,213 infants with first trimester bupropion exposure, and showed no increase in the risk of any congenital malformation compared with other antidepressant exposures in the first trimester, or with bupropion exposure outside of the first trimester.<sup>121</sup> Thus far, studies of venlafaxine and mirtazapine have not shown increased risk of congenital malformations.<sup>95,127,128</sup>

The potential for confounding by indication and detection bias in studies of antidepressant use during pregnancy and MCM risk has received intense focus. At least one very

**Table 2** Meta-analyses of observational studies of antenatal AD use and the risk of congenital malformations

Reference	Studies, n	Exposure groups	Main results	Confounding and bias
Myles et al <sup>105</sup>	Major malformations: 16 Minor malformations: 4	SSRI, first trimester (n=23,919) No SSRI	Any malformation: all SSRIs, OR 1.10 (95% CI 1.03–1.16); paroxetine, OR 1.29 (95% CI 1.11–1.49); fluoxetine, OR 1.14 (95% CI 1.01–1.30); sertraline, OR 1.01 (95% CI 0.88–1.17); citalopram, OR 1.04 (95% CI 0.92–1.17)	Separate analyses conducted for studies that considered early versus continuous SSRI exposure; controlled for tobacco, alcohol, or illicit drug use; controlled for maternal age; controlled for maternal parity; and exclusion of chromosomal or genetic abnormalities.
Grigoriadis et al <sup>107</sup>	12	Any AD (n=17,915) No AD	Any malformation: RR 0.93 (95% CI 0.85–1.02) Major malformations: RR 1.07 (95% CI 0.99–1.17)	Systematic Assessment of Quality in Observational Research (SAQOR) tool used to evaluate individual study quality.
Riggin et al <sup>108</sup>	21	Fluoxetine, first trimester (cohort studies, n=11,225; case-control studies, n=9,800)	Any malformation: cohort studies, OR 1.12 (95% CI 0.98–1.28); case-control studies, OR 3.72 (95% CI 0.74–18.79)	
Bar-Oz et al <sup>106</sup>	6	Paroxetine, first trimester (n=2,621) No paroxetine AD exposure No teratogen exposure	Paroxetine versus other AD or known nonteratogens: Any malformation: OR 1.31 (95% CI 1.03–1.67) Paroxetine versus other AD: Any malformation: OR 1.30 (95% CI 0.92–1.80) Paroxetine versus known nonteratogens: Any malformation: OR 1.54 (95% CI 0.99–2.41)	Diagnostic tests in pregnancy: Significantly greater use in AD users versus nonusers; no significant difference between paroxetine and other AD, using population-based registry data. Diagnostic tests in infancy: Significantly higher rates of echocardiograms with in utero SSRI exposure versus no AD exposure, using population-based registry data. Indication: Significantly higher proportion of use for anxiety disorders with paroxetine versus other SSRIs.
Rahimi et al <sup>109</sup>	9	SSRI, any exposure during pregnancy (n=1,102) Unexposed to SSRI	Any major malformation: OR 1.39 (95% CI 0.91–2.15)	
Addis et al <sup>110</sup>	4	Fluoxetine, first trimester (n=367)	Any major malformation: weighted average 2.6% (95% CI 1%–4.2%)	

**Abbreviations:** SSRI, selective serotonin-reuptake inhibitor; OR, odds ratio; CI, confidence interval; RR, relative risk; AD, antidepressant.

large population-based study suggested that the apparent increase in cardiac malformation risk associated with SSRIs also existed among depressed women who did not undergo drug treatment.<sup>116</sup> However, this point remains controversial, because of findings from other studies that suggest that SSRIs, not maternal depression, may account for complications.<sup>6</sup> One report has raised the possibility that higher risk of cardiac defects with paroxetine and other SSRIs may be due to detection bias. In that study, women who took SSRIs during pregnancy had 30% more prenatal ultrasound exams than women who did not take an antidepressant, while infants who had been exposed to SSRIs during pregnancy had twice as many echocardiograms in the first year of life than unexposed infants.<sup>106</sup>

In summary, antidepressants in general and SSRIs more specifically have not been consistently associated with an increased risk of major congenital malformations overall.

However, there appears to be a small but statistically significant risk for cardiovascular malformations (mainly septal defects) with some individual agents, such as paroxetine, and possibly also fluoxetine. Contradictory findings and additional factors make the overall literature difficult to translate to clinical practice. For example, the absolute risk with SSRIs for any cardiovascular malformation appears small, and may be susceptible to confounding (including confounding by indication) and detection bias.<sup>99,129</sup> Even if the relationship between SSRIs and heart defects is causal, it is still not established if any specific agents are clearly safer than others, although paroxetine and fluoxetine have been most implicated as having higher risk than other SSRIs. Moreover, grouping together all cardiovascular or cardiac defects limits clinical translation because of the wide variety of defects under consideration that are expressed along a broad spectrum of severity and medical risk. It is unclear, for instance,

**Table 3** Meta-analyses of observational studies of antenatal AD use and the risk of cardiac malformations

Reference	Studies, n	Exposure groups	Main results	Confounding and bias
Myles et al <sup>105</sup>	9	SSRI, first trimester (n=22,412) No SSRI	Any cardiac malformation: OR 1.15 (95% CI 0.99–1.32); paroxetine OR 1.44 (95% CI 1.12–1.86); fluoxetine 1.25 (95% CI 0.98–1.60); sertraline OR 0.93 (95% CI 0.70–1.24); citalopram OR 1.03 (95% CI 0.80–1.32) Any cardiovascular malformation: RR 1.36 (95% CI 1.08–1.71); paroxetine RR 1.43 (95% CI 1.08–1.88); fluoxetine RR 1.17 (95% CI 0.89–1.55) Septal heart defects (any): RR 1.40 (95% CI 1.10–1.77) Ventral septal defects: RR 1.54 (95% CI 0.71–1.33) Any cardiac malformation: cohort studies, OR 1.6 (95% CI 1.31–1.95); case-control studies OR 0.63 (95% CI 0.39–1.03)	Separate analyses conducted for studies that considered early versus continuous SSRI exposure; controlled for tobacco, alcohol, or illicit drug use; controlled for maternal age; controlled for maternal parity; and exclusion of chromosomal or genetic abnormalities. Systematic Assessment of Quality in Observational Research (SAQOR) tool used to evaluate individual study quality.
Grigoriadis et al <sup>107</sup>	Any cardiovascular malformation: 13 Septal heart defects: 9 Ventral septal defects: 5	Any AD (n=22,537) No AD		
Riggin et al <sup>108</sup>	16	Fluoxetine, first trimester (cohort studies, n=7,874; case-control studies, n=13,346)		
Bar-Oz et al <sup>106</sup>	Meta-analysis RC: 4 CC: 2	Paroxetine, first trimester (n=5,332) Nonparoxetine AD exposure No teratogen exposure	Paroxetine versus other AD or known nonteratogens: Cardiac malformation (any): OR 1.72 (95% CI 1.22–2.42) Paroxetine versus other AD: Cardiac malformation (any): OR 1.70 (95% CI 1.17–2.46) Paroxetine versus known nonteratogens: Cardiac malformation (any): OR 3.47 (95% CI 0.90–12.21)	Diagnostic tests in pregnancy: Significantly greater use in AD users versus nonusers; no significant difference between paroxetine and other AD, using population-based registry data. Diagnostic tests in infancy: Significantly higher rates of echocardiograms with in utero SSRI exposure versus no AD exposure, using population-based registry data. Indication: Significantly higher proportion of use for anxiety disorders with paroxetine versus other SSRIs.
Rahimi et al <sup>109</sup>	8	SSRI, any exposure during pregnancy (n=906) Unexposed to SSRI	Cardiovascular malformation: OR 1.19 (95% CI 0.53–2.68)	

**Abbreviations:** SSRI, selective serotonin-reuptake inhibitor; OR, odds ratio; CI, confidence interval; RR, relative risk; AD, antidepressant; RC, retrospective cohort study; CC, case control study.



if SSRIs are associated with the development of more severe forms of septal defects, including those requiring surgical management, or if in utero exposure to antidepressants affects rates of spontaneous septal defect closure. For non-SSRI antidepressants, MCM-risk estimates are even less clear. A potential relationship between clomipramine exposure and fetal cardiac defects requires further examination.

### Minor congenital malformations

The term “minor congenital malformation” refers to congenital birth defects that have no major surgical or cosmetic importance. Very few studies to date have focused on the risk of minor congenital malformations associated with antidepressant use during pregnancy. Chambers et al reported no significant association between antenatal fluoxetine use and MCMs,<sup>101</sup> but also reported an increased number of exposed neonates that manifested three or more minor congenital anomalies. In a subsequent paper by Wisner et al, neither exposure to SSRIs nor maternal depression was associated with increased risk of minor physical anomalies.<sup>51</sup> A recent meta-analysis of heterogeneous studies (2,631 exposed pregnancies) showed no statistically significant increase in the risk of minor congenital malformations with SSRIs (OR 1.16, 95% CI 0.79–1.71).<sup>105</sup> The small overall sample size did not permit additional analyses of risk by individual drug.

Results of existing studies of antidepressants and the risk of minor congenital malformations can be interpreted as reassuring thus far. Although the medical significance of a given minor malformation may be limited, they are not medically inconsequential. Some minor malformations serve as risk markers for the presence of an occult MCM, particularly if three or more minor malformations are present.<sup>130</sup> As such, additional studies of minor congenital malformation risk associated with maternal use of antidepressants during pregnancy are needed.

### Adverse neonatal events

#### Persistent pulmonary hypertension of the newborn

PPHN is caused by a failure of normal circulatory transition from a state of relatively high pressure in the pulmonary circulation before birth (to facilitate gas exchange at the placenta) to normal pulmonary artery pressure after delivery (to facilitate pulmonary gas exchange). If the normal decrease in pulmonary vascular tone does not occur, PPHN leading to hypoxemia results because of continued shunting of blood away from the lungs. Although PPHN is rare (one to two cases per 1,000 live births), severe cases are

life-threatening.<sup>131</sup> Risk factors for PPHN include cesarean delivery, maternal African American or Asian race, high maternal pregravid body mass index ( $>27$  kg/m<sup>2</sup>), maternal diabetes mellitus, maternal asthma, maternal smoking, neonatal sepsis, meconium aspiration, and gestational age 34–37 weeks and  $>41$  weeks.<sup>132</sup>

A potential association between late-pregnancy exposure to fluoxetine and PPHN was initially reported in a small prospective cohort study of 228 exposed pregnancies and 254 control pregnancies with no antenatal fluoxetine exposure.<sup>86</sup> An increased risk of PPHN was observed with late- versus first trimester fluoxetine exposure (2.7% versus 0%). A subsequent multicenter case-control study by Chambers et al involving 377 women whose infants had PPHN and 836 matched control mother–infant pairs found a sixfold-increased risk of PPHN with in utero SSRI exposure after 20 weeks’ gestation (adjusted OR 6.1, 95% CI 2.2–16.8).<sup>101</sup> Neither SSRI exposure prior to the 20th gestational week nor exposure to non-SSRI antidepressants at any point during pregnancy was associated with increased risk of PPHN. The first of two retrospective analyses of Swedish Medical Birth Register data found an association between maternal SSRI use during the early stages of pregnancy and PPHN (relative risk [RR] 2.4, 95% CI 1.2–4.3) after adjusting for maternal age, first parity, maternal body mass index, and smoking.<sup>133</sup> A more recent analysis of that data included antenatal exposures to SSRIs and non-SSRI antidepressants, and showed an increase in the risk of PPHN associated with antidepressant use in both early (RR 2.30, 95% CI 1.29–3.80) and later stages of pregnancy (RR 2.30, 95% CI 1.17–4.85).<sup>94</sup>

The FDA responded to the initial positive report by issuing a public health advisory in 2006 about an increased risk of PPHN associated with maternal SSRI use after the 20th gestational week.<sup>134</sup> However, subsequent results of a retrospective cohort study of 1,104 infants exposed to antidepressants during the third trimester<sup>135</sup> and a retrospective chart review of 24,214 deliveries (808 of which involved antepartum SSRI exposure)<sup>96</sup> did not find an association between antenatal SSRI exposure and PPHN. In a large case-control study of 11,923 births (20 with primary PPHN), cesarean delivery prior to the onset of labor, but not in utero SSRI exposure after 20 weeks’ gestation, was significantly associated with PPHN.<sup>136</sup> The largest study to date based on health registry data from five Scandinavian countries (1,618,255 singleton births) identified 33 PPHN cases among 11,014 late-pregnancy SSRI exposures, or approximately three per 1,000 infants, compared with the background

PPHN rate of one to two per 1,000 births (adjusted OR 2.1, 95% CI 1.5–3.0).<sup>137</sup>

In sum, it is unclear if late SSRI exposure increases the risk of PPHN, a rare but potentially serious adverse neonatal outcome. Results of positive studies have indicated an approximate two- to 2.5-fold increased risk of PPHN; however, the absolute risk appears to be very small, and the potential association between in utero antidepressants and PPHN remains controversial. If causal, the absolute risk has been estimated as three to 12 affected newborns per 1,000.<sup>101,137</sup> Based in part on negative findings from more recent studies, the FDA has revised its original position, concluding that it is premature to reach definitive conclusions regarding the risk of PPHN with SSRI use in pregnancy.<sup>138</sup>

### Poor neonatal adaptation syndrome

The term “poor neonatal adaptation syndrome” (PNAS) refers to a constellation of behaviors and clinical signs observed in neonates (irritability, agitation, tremors, jitteriness, shivering, increased muscular tone, digestive disturbances or feeding difficulties, and respiratory distress) that has been linked with late-third trimester exposure to SSRIs and other antidepressants. PNAS is transient and generally mild in severity, requiring supportive care only. More severe cases may require that initial recovery take place in a neonatal intensive care unit.<sup>139,140</sup> The pathophysiology of PNAS is thought to involve either a serotonergic rebound effect (analogous to discontinuation syndromes observed in adults who undergo abrupt withdrawal of serotonergic antidepressants) or direct serotonergic toxicity.<sup>140,141</sup>

An early description of PNAS was provided by Chambers et al, who observed increased rates of neonatal respiratory problems, cyanosis with feeding, jitteriness, and special care nursery admission associated with third trimester exposure to fluoxetine.<sup>86</sup> Oberlander et al reported on the incidence of transient neonatal complications associated with second and third trimester exposure to SSRIs, with or without concomitant antenatal exposure to benzodiazepine or clonazepam, among 46 exposed and 23 unexposed newborns.<sup>142</sup> Transient irritability, jitteriness, hypothermia, sleep disruption, increased muscle tone, hypothermia, and initial lack of crying were observed in nearly 30% of exposed neonates. Others have provided evidence of PNAS associated with antenatal use of TCAs and SNRIs.<sup>97,133,143–147</sup> Overall, the risk of PNAS appears to be similar between late pregnancy exposure to TCA, SNRIs, and SSRIs.<sup>148,149</sup>

A meta-analysis<sup>150</sup> of prospective studies that examined adverse fetal and neonatal effects associated with antenatal

antidepressant exposure (totaling 1,066 mother–infant pairs) showed a trend-level association in the primary analysis between third trimester SSRI exposure and PNAS that became significant after including results of a large study<sup>151</sup> that included infants with in utero SSRI exposure during the first and third trimesters (OR 1.99, 95% CI 1.43–2.77). A more recent meta-analysis of 12 studies (3,780 exposed infants) showed significantly increased risk of PNAS (OR 5.07, 95% CI 3.25–7.90), infant respiratory distress (OR 2.20, 95% CI 1.81–2.66), and tremors (OR 7.89, 95% CI 3.33–18.73).<sup>152</sup>

Although not all studies are in agreement,<sup>153,154</sup> the published literature appears to be more consistent with regard to a statistically and clinically significant association between antenatal antidepressant exposure during late pregnancy and the risk of PNAS, which may occur in 10%–30% of neonates with third trimester exposure to SSRIs or SNRIs.<sup>155,156</sup> To limit the risk of PNAS occurrence, the FDA issued a recommendation in 2004 that health care providers consider tapering antidepressants used during the third trimester.<sup>157</sup> However, the effectiveness of this practice for reducing the risk of PNAS has not been established in controlled studies. One population-based study of 119,547 birth records that compared the risk of adverse neonatal outcomes according to fetal antidepressant-exposure status during the last 14 days of pregnancy showed no difference in the risk of developing clinical signs of PNAS between infants in the exposed group and propensity score-matched controls.<sup>158</sup> Further research is needed in order to determine whether suspension of effective antidepressant treatment during the late-third trimester reduces the risk of PNAS without increasing the risk of maternal depressive relapse, particularly during the postpartum period.

### Adverse obstetric outcomes

#### Premature delivery

Premature delivery refers in general terms to the birth of an infant at <37 weeks gestational age, although prematurity can also refer to the birth of an infant before vital organs have developed sufficiently to allow postnatal survival. It is often used synonymously with a related term, preterm delivery (which refers only to delivery prior to 37 weeks' gestation), and occasionally with early preterm delivery (eg, delivery prior to 34 weeks' gestation). Regardless, decreased gestational age at delivery has been associated with increased neonatal morbidity and mortality compared with term-born children.<sup>159,160</sup> One meta-analysis of 15 studies estimated the effects on antenatal antidepressant use on gestational age at

delivery, and found a small but statistically significant difference between antidepressant-exposed and -unexposed babies (standardized mean difference [SMD]  $-0.23$ , 95% CI  $-0.34$  to  $-0.12$ ).<sup>161</sup> As referenced by the authors, this equates clinically with a difference in gestational age of 2–3 days.

With regard to premature delivery as a discrete outcome, observational studies have documented an increased risk associated with antenatal antidepressant exposure.<sup>87,162–165</sup> However, not all studies are in agreement,<sup>89,90,92,100,166,167</sup> and one study even documented a reduced risk of spontaneous preterm birth associated with medication treatment of depressive symptoms during pregnancy, although the main exposure group included both sedative medications and antidepressants.<sup>32</sup> Most studies to date have focused on antenatal SSRI use; however, an increased risk of preterm delivery has also been reported for TCAs, venlafaxine, and mirtazapine.<sup>97,127,128</sup>

Whether or not an association between maternal antidepressant exposure and the risk of premature delivery is causal or confounded by underlying maternal depression has also been investigated, and is an ongoing focus of clinical debate.<sup>168,169</sup> A prospective cohort study documented a higher risk of preterm delivery with continuous exposure to SSRIs or maternal depression across gestation compared with partial or no exposure.<sup>51</sup> Another prospective study found significantly higher rates of premature delivery and special care nursery admissions in infants born to women with antenatal depression treated with antidepressants (predominantly SSRIs) compared with antenatally depressed women with no antidepressant or only limited antidepressant use and nondepressed controls.<sup>170</sup> An inverse relationship between antidepressant dose and gestational age at delivery was observed. A very recent cohort study of 2,793 pregnant women documented an increased risk of preterm birth associated with SSRIs with or without a major depressive episode, while no increase in risk was observed for major depressive episode without SSRI use.<sup>171</sup> Moreover, a recent meta-analysis of 14 studies found an increased risk of preterm delivery associated with maternal antidepressant use during pregnancy (pooled OR 1.55, 95% CI 1.38–1.74).<sup>161</sup> Comparisons of depressed mothers with and without antidepressant exposure (five studies) showed a trend-level association with similar effect size as that of the main analysis (pooled OR 1.58, 95% CI 0.97–2.56), suggesting that the effect of antenatal antidepressant exposure on the risk of premature delivery may be independent of maternal depression. Others, however, have documented significantly higher rates of preterm delivery with antenatal SSRI exposure that attenuated after controlling

for factors that may serve as proxy indicators of maternal depression severity and psychiatric comorbidity.<sup>6,171</sup>

In summary, there is evidence of an increased incidence of preterm delivery associated with maternal antidepressant use in some studies and a greater risk of preterm delivery in the most recent meta-analysis addressing this topic, but it is still unclear whether maternal antidepressant use increases the risk of premature delivery independently of other factors. Maternal depression severity and psychiatric comorbidity may serve as important sources of confounding in existing studies.

### Spontaneous abortion

Spontaneous abortion refers to the loss of a fetus prior to the 20th gestational week in the absence of an elective termination of pregnancy or other outside intervention. Spontaneous abortion is thought to occur in 12%–15% of diagnosed pregnancies,<sup>172</sup> with higher rates (approaching 40%) in pregnant women over the age of 40 years.<sup>172</sup> Chromosomal abnormalities are the leading cause of spontaneous abortions, while thrombotic events leading to inadequate fetal blood supply and adverse maternal health factors are less common causes.<sup>172,173</sup> Spontaneous abortion has been linked with both maternal depression<sup>174</sup> and maternal use of various antidepressants during pregnancy, including SSRIs, venlafaxine, and other agents.<sup>90,103,120,127,174–178</sup> Other findings from mainly small prospective cohort studies have been negative.<sup>86,89,179,180</sup>

Three meta-analyses document small increases in the risk of spontaneous abortion associated with maternal antidepressant use during pregnancy. Hemels et al conducted a meta-analysis of six homogeneous cohort studies (1,534 exposed pregnancies) and reported a pooled RR of 1.45 (95% CI 1.19–1.77) and an increase in risk of 3.9% (95% CI 1.9%–6.0%) among antidepressant-exposed pregnancies versus matched control pregnancies.<sup>174</sup> A subsequent meta-analysis of nine nonheterogeneous studies (five of which reported on rates of spontaneous abortion in 1,900 exposed pregnancies) by Rahimi et al reported a summary OR of 1.7 (95% CI 1.28–2.24).<sup>109</sup> The majority of reviewed studies did not adequately address important confounding factors, including history of miscarriage, rates of induced abortion, maternal age, and severity of maternal depression.<sup>126,181</sup> The most recent meta-analysis by Ross et al included three studies that met prespecified quality-assessment criteria (1,503 exposed pregnancies), and generally supported the conclusions of earlier meta-analyses by reporting a pooled OR of 1.47 (95% CI 0.99–2.17).<sup>161</sup> Comparison with a

depressed but antidepressant-unexposed control group was not possible, owing to a lack of data.

Not included in the meta-analyses was a very recent population-based retrospective cohort study using data from all identified pregnancies in Denmark (1997–2008), 22,061 of which involved evidence of antenatal antidepressant use and 1,843 of which included a diagnosis of depression but no evidence of antenatal antidepressant use.<sup>182</sup> A total of 2,637 (12.0%) cases in the antidepressant-exposed group and 1,843 (11.4%) in the depressed but nonexposed group ended in spontaneous abortion (RR 1.14, 95% CI 1.10–1.18). However, after restricting the analysis to women with a registry-based diagnosis of depression, the adjusted RR for spontaneous abortion with antenatal antidepressant exposure was 1.00 (95% CI 0.80–1.24). No individual SSRIs were associated with spontaneous abortions; however, venlafaxine (RR 1.80, 95% CI 1.19–2.72), duloxetine (RR 3.12, 95% CI 1.55–6.31) and mirtazapine (RR 2.23, 95% CI 1.34–3.70) were associated with an increased risk of spontaneous abortion.

In sum, available studies suggest that antenatal antidepressant use (including SSRIs) may be associated with a small but statistically significant increase in the risk of spontaneous abortion. However, conclusions from available studies are contradictory, and the validity of the small effect sizes documented in meta-analyses and most individual studies are threatened by possible confounding. Many studies did not adequately control for important risk factors for spontaneous abortion, including history of miscarriage, maternal age, maternal smoking status, severity of maternal depression, concomitant psychiatric disorders (including substance-use disorders), other diagnoses for which antidepressants may be prescribed, and maternal use of other medications that may also elevate the risk of spontaneous abortion.<sup>126</sup> The larger risk estimates documented for some non-SSRI antidepressants<sup>176,178,182</sup> may reflect greater severity of underlying depression, since these agents are not generally considered immediate first-line therapeutic options. Moreover, many studies did not clearly distinguish between spontaneous and induced abortions,<sup>161,181</sup> which could have resulted in biased estimates of spontaneous abortion risk with antidepressant use, given that maternal depression itself may increase the risk of elective termination of pregnancy.<sup>183,184</sup>

#### Poor infant growth and low birth weight

Several observational studies have documented small increases in the risk of low birth weight for gestational age with maternal antidepressant use during pregnancy.<sup>6,86,100,151,162,164,185</sup>

Others have documented linear decreases in gestational age associated with higher antidepressant doses used during pregnancy,<sup>170</sup> or increased risk of low birth weight associated with high doses of fluoxetine taken throughout pregnancy.<sup>102</sup> However, the majority of individual published studies have been negative,<sup>51,90,100,127,153,175,179,186–192</sup> and one study documented a possible increase in the risk of large birth weight with the use of TCAs early in pregnancy.<sup>87</sup>

Underlying maternal depression and anxiety disorders have also been associated with poor infant growth and low birth weight,<sup>6,30,31,33–37</sup> raising the possibility that the relationship between maternal antidepressant use during pregnancy and the risk of low birth weight or poor fetal growth may be confounded by antidepressant indication. However, few studies accounted for maternal depression diagnosis or depression severity, or risk factors for low birth weight that may correlate significantly with maternal depression, such as smoking, alcohol use, and suboptimal maternal weight gain during pregnancy.<sup>17,126,193–195</sup> Even for studies that did account, at least partially, for these factors, results are mixed. For example, in one prospective cohort study of 174 pregnant women (46 of whom took an SSRI during pregnancy, 31 of whom were diagnosed with major depression but did not take an SSRI during pregnancy, and 97 of whom were exposed to neither depression nor an SSRI during pregnancy), no significant associations between antenatal SSRI exposure or antenatal depression and infant weight, head circumference, or length were observed compared with no antenatal exposure to SSRIs or depression.<sup>196</sup> By contrast, a small case-control study of 27 pregnant women who took antidepressant medications for diagnosed major depression and 27 matched controls with depression severity assessed using the Beck Depression Inventory (second edition)<sup>197</sup> showed an increased risk of low birth weight (OR 8.33, 95% CI 1.11–62.67) and significantly lower postpartum body weight, length, and head circumference measured at 1 month postdelivery with antenatal antidepressant exposure.<sup>165</sup> There was no significant association between depressive symptoms, smoking, or alcohol use and risk of low birth weight or subsequent infant-growth measures, suggesting an independent effect of medication exposure.

A recent meta-analysis of 20 studies (over 5,000 exposed pregnancies) with moderate heterogeneity reported a small SMD in birth weight between infants with in utero antidepressant exposure and those with no such exposure (SMD –0.10, 95% CI –0.16 to –0.03), corresponding to a difference of –74 g (95% CI –117 to –31 g).<sup>161</sup> After restricting the control group to infants born to depressed mothers with no antidepressant

exposure, the SMD in birth weight was nearly zero and not statistically significant (SMD  $-0.02$ , 95% CI  $-0.10$  to  $0.06$ ).

In sum, maternal antidepressant use during pregnancy may be associated with small decreases in birth weight, but maternal depression may mediate this relationship. Furthermore, data from the most recent meta-analysis suggest that the average difference in birth weight between antidepressant-exposed and -unexposed babies is approximately 74 g, or  $\sim 0.16$  lb.<sup>161</sup> The clinical significance of such a small difference in birth weight may be questionable, especially for birth weights that still fall within the normal range.

### Preeclampsia

Gestational hypertension (blood pressure  $\geq 140/90$  mmHg on at least two separate readings spaced  $\geq 6$  hours apart after 20 weeks' gestation occurring in women who were normotensive before pregnancy) and preeclampsia (gestational hypertension accompanied by proteinuria) collectively refer to a spectrum of hypertensive conditions that develop during pregnancy, with or without accompanying organ dysfunction.<sup>198</sup> Approximately half of gestational hypertension cases that develop prior to 30 weeks' gestation will progress to preeclampsia.<sup>198</sup> Maternal and perinatal outcomes related to mild gestational hypertension and preeclampsia are similar to those of normotensive pregnancies.<sup>199</sup> Severe gestational hypertension, on the other hand, is associated with higher rates of cesarean delivery, placental abruption, and preterm delivery, while severe preeclampsia is associated with greater risk of perinatal mortality, placental abruption, and severe maternal morbidity and mortality compared with unaffected pregnancies.<sup>200,201</sup> Risk factors for gestational hypertension and preeclampsia include advanced maternal age, nulliparity, history of hypertension or renal disease, obesity, family or personal history of preeclampsia, multifetal gestation, and history of diabetes.<sup>198</sup> More recently, maternal depression and anxiety disorders<sup>202,203</sup> and greater depression severity<sup>204</sup> have been shown to increase the risk of developing preeclampsia, independently of the effects of maternal age, race, and pregravid body mass index.

A potential link between maternal antidepressant use during pregnancy and gestational hypertension, preeclampsia, or the two combined has been suggested. A cohort study by Qiu et al of pregnant women with a mood or anxiety disorder diagnosis showed a modest but not statistically significant increase in the risk of gestational hypertension associated with maternal use of SSRIs (OR 1.81, 95% CI 0.69–4.75) and SSRIs with adjunctive non-SSRI psychotropic medications (mainly TCAs and benzodiazepines, OR 2.88,

95% CI 0.40–20.98).<sup>202</sup> However, this study had low statistical power, and was not designed to investigate the effect of antidepressants on the risk of preeclampsia. Retrospective studies using much-larger cohorts have reported significant associations between maternal antidepressant use during pregnancy and the risk of gestational hypertension and/or preeclampsia.<sup>94,205</sup> One nested case-control study that focused on the risk of gestational hypertension associated with use of antidepressants during pregnancy documented a significant increase in risk associated with general use of antidepressants (OR 1.52, 95% CI 1.10–2.09) and with SSRIs (OR 1.53, 95% CI 1.01–2.33) and paroxetine (OR 1.81, 95% CI 1.02–3.23) in stratified analyses.<sup>206</sup> A large retrospective cohort study of 69,448 pregnancies in women with insurance claim-based diagnoses of depression found increased risk of preeclampsia associated with SSRI (RR 1.22, 95% CI 0.97–1.54), SNRI (RR 1.95, 95% CI 1.25–3.03), and TCA monotherapy (RR 3.23, 95% CI 1.87–5.59) compared with no antidepressant use.<sup>207</sup> Similar findings were reported in comparisons between cohort members with evidence of continuous antidepressant use during pregnancy and those with evidence of antidepressant discontinuation during gestational weeks 10–24 or beyond.

In summary, available evidence suggests that pregnant women treated with antidepressants are at higher risk for gestational hypertension and preeclampsia. This includes evidence of a possible effect independent of underlying maternal depression or anxiety disorder diagnoses; however, existing studies do not address confounding by depression severity. On the one hand, findings of increasing risk of preeclampsia with SNRIs and TCAs may not be that surprising, since the choice to use these medications over first-line treatments in pregnancy may reflect greater symptom burden and treatment resistance. These findings are noteworthy, given the risk of blood pressure increases that can occur during treatment with SNRIs and selected TCAs.<sup>208–210</sup> Importantly, it is still unclear if antenatal antidepressant exposure is associated with severe (rather than mild) gestational hypertension or preeclampsia specifically.

### Neurodevelopmental and behavioral outcomes

Several studies have examined the risk of impaired long-term neurobehavioral and cognitive development in children exposed in utero to antidepressants. Most studies have focused on the potential effects of SSRIs and SNRIs. In general, the majority of reports are from small prospective cohort studies that have shown no significant effect of maternal antenatal

antidepressant use on global IQ, temperament, or language, motor, or behavioral development in offspring.<sup>43,186,189,211,212</sup> Two prospective studies showed that poor neonatal adaptation associated with antidepressant exposure in utero was not associated with subsequent developmental impairments.<sup>44,142</sup> In two of the reviewed studies, maternal depression, maternal depression severity during pregnancy, and the number of depressive episodes after delivery were identified as risk factors for poorer behavioral, cognitive, and language development in offspring.<sup>43,44</sup> Follow-up studies of TCA-exposed babies have also shown normal motor, behavioral, and cognitive development.<sup>43,144,189</sup>

On the other hand, Casper et al reported a significantly higher prevalence of subtle problems with motor development and control and lower Apgar scores in offspring (up to 40 months of age) of depressed mothers who received SSRI treatment during pregnancy (31 exposed pregnancies) compared with babies of mothers diagnosed with major depression not treated with medications during pregnancy.<sup>153</sup> Alcohol consumption was reported more frequently among the exposed pregnancies. An analysis of data from the Danish National Birth Cohort that included 415 pregnancies with second or third trimester antidepressant use and 489 pregnancies with maternal depression but no antidepressant use showed delayed motor development in offspring from exposed pregnancies as assessed by telephone interview, although time required to sit and walk still fell within the normal range of development.<sup>213</sup> Children of antidepressant-treated mothers were at significantly higher risk of not being able to sit without support at 6 months of age (OR 2.1, 95% CI 1.23–3.60) or occupy themselves at 19 months of age (OR 2.1, 95% CI 1.09–4.02). Neither study was able to evaluate the effects of individual medications. Finally, a meta-analysis of observational studies reporting the effects of maternal antidepressant use on 1-minute (ten studies) and 5-minute Apgar scores (14 studies) found small but statistically significant differences between antidepressant-exposed and -unexposed babies at 1 minute (SMD -0.19, 95% CI -0.30 to -0.08) and 5 minutes (SMD -0.33, 95% CI -0.47 to -0.20).<sup>161</sup> As pointed out by the authors, this equates clinically with a difference in Apgar score of about 0.5 point at each time point.

In summary, relatively few studies have been conducted that focus on the effects of in utero antidepressant exposure on neurobehavioral, cognitive, and motor development. Most studies focused on such outcomes shortly after delivery or during early childhood. Few data are available regarding whether or not these outcomes related to cognitive or behavioral functioning persist later in life.<sup>214</sup> Many studies

did not adequately control for the potential effects of maternal IQ, socioeconomic status, fetal exposure to alcohol and nicotine, duration and severity of maternal depression, and other concomitant fetal medication exposures that can also impact brain development. Data on the effects of individual antidepressant medications are also lacking. Further studies are needed to assess the independent effects of individual antidepressant medications on both early and later childhood neurobehavioral, cognitive, and motor development.

## Summary and practical implications

Clinicians who treat women with antenatal depression are fortunate to have a large number of pharmacological and nonpharmacological therapeutic tools at their disposal. In spite of the wide range of treatment options and increasing recognition of the adverse effects of untreated or undertreated antenatal depression, rates of psychiatric treatment among pregnant and postpartum women with mood disorders, including major depression, are very low.<sup>215</sup> Even when women are appropriately screened, research suggests that more than 80% of women with antenatal depression do not receive treatment.<sup>5</sup> This is particularly troubling in view of the accumulating evidence suggesting that successful treatment of maternal depression leads to better outcomes for both mothers and their children, particularly if remission of depressive symptoms can be achieved.<sup>48,49,216–219</sup>

It is important to recognize that several pragmatic challenges make treating antenatal depression very difficult. First, there is little information about the comparative effectiveness of many of the most commonly employed therapeutic modalities for treating major depression in pregnant women, and many patients who receive treatment with psychotherapy or antidepressant medications – whether pregnant or not – do not benefit, or experience only modest improvement in depressive symptoms and functioning. The pregnancy and developing fetus are therefore still exposed to the potentially harmful effects of residual depressive symptoms in many cases, and we are not yet able to predict with acceptable certainty which pregnant women are more likely to benefit from a given set of treatments.

Second, particularly with respect to the potential harms associated with treating antenatal depression with antidepressants, a great deal of experience and skill is required to interpret a conflicting and in some cases controversial medical literature made up almost entirely of observational studies with increasingly complex designs and statistical approaches. The complex designs and statistical approaches are needed to reduce, or at least limit to the greatest extent possible, the effects of confound-

ing and bias inherent in nonrandomized studies. However, they also make studies more difficult to interpret, and most clinicians lack the advanced methodological training to do so. Because observational studies cannot firmly establish causal links between antidepressant use during pregnancy and adverse obstetric or fetal outcomes, no single study can be regarded as definitive. This does not mean that observational studies cannot yield data of sufficient quality to inform clinical practice. Arguments in favor of causality can be made with consistent replication of findings across numerous studies from different populations. However, this does mean that clinicians must invest considerable effort to familiarize themselves with the large volume of existing literature and stay up to date with the newest published data. The increasing time demands and rigors of daily practice erode and work against many clinicians' ability to maintain this capability.

In spite of these challenges, we believe existing literature and clinical practice guidelines do provide useful guidance.<sup>16</sup> First, it is helpful to remember that although this review is focused on major depression, not all antenatal depression is major depressive disorder. Depressive symptoms characterize a large number of conditions that can arise during pregnancy, ranging from nonspecific reactions to stressors to major affective syndromes, including major depression and bipolar (type I or II) depression. This is not to say that other forms of maternal depression are unimportant; indeed, other depressive states and even high levels of maternal stress during pregnancy can adversely affect fetal and birth outcomes,<sup>220</sup> and many physical symptoms overlap between major depression and pregnancy, such as fatigue, sleep disruption, weight change, and concentration difficulties.<sup>221</sup> Although treatment for nonspecific or poorly characterized depressive states may be required to protect against their potential adverse effects, there is currently little or no high-quality evidence supporting the use of antidepressants or other therapies for nonspecific or poorly characterized depressive states. On the other hand, the use of antidepressants and/or structured psychotherapies for patients with a firm diagnosis of major depression in general and severe major depression in particular is clearly supported.

In addition to establishing the diagnosis of major depression, factors that bear on treatment selection and likelihood of antepartum depression relapses (for those with existing diagnoses of major depression) must also be assessed. Assessment of the former includes, at minimum, evaluation of current depressive symptom severity and impact on daily functioning, history of treatment(s) and treatment response, availability of treatment resources, medical and obstetric history, and patient preference.<sup>220</sup> Additional factors that drive

treatment selection include duration, recurrence, and severity of depressive symptoms during past depressive episodes; history of self-harm tendencies; comorbid psychiatric and substance-use disorders (including alcohol, drugs of abuse, and tobacco: currently, during periods of active depression treatment, and when not receiving treatment); quality and availability of social supports; family history of major depression and treatment response; family situation; and evidence of domestic abuse or violence. Risk factors for depressive relapse during pregnancy include longer illness duration, history of recurrent illness, history of suicidality, family history of depressive illness, lack of social support, comorbid anxiety disorders, existing or impending single parenthood, low socioeconomic status, unintended pregnancy, exposure to domestic violence, and ongoing stressful life events.<sup>50,221</sup>

Because maternal major depression can respond positively to pharmacotherapy, psychotherapy, and other interventions, and because no single intervention is uniformly successful or devoid of risk, it is perhaps ideal for clinicians to avoid the "simple" choice of whether or not to treat antenatal depression with antidepressants in favor of beginning with a broad list of reasonable therapeutic options. Such a list can be generated by considering what treatments would have the highest chance of achieving remission in an individual patient, given a thorough assessment of the factors listed earlier. This may include nonpharmacological treatments only, antidepressant medication only, or a combination of these. As such, the initial list may be quite large, particularly for patients with limited treatment histories. Each option can be discussed with the patient and support system, mindful that there are no guarantees of positive outcome. The initial list of options can then be narrowed based on relative obstetric and fetal safety of each available service, clinical factors, and individual patient values and concerns. Fully informed decision making requires that the risks of both untreated maternal depression and the risks associated with each proposed intervention be reviewed, and that all reasonable treatment options be discussed.

## Disclosure

The authors report no conflicts of interest in this work. In the past, Dr Bobo has received grants/research support from Cephalon and has served on speaker panels for Janssen Pharmaceutica and Pfizer.

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